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Longer Brainstem Auditory Evoked Response Latencies of Individuals With Fragile X Syndrome Related to Sedation

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Brainstem auditory evoked response latencies were studied in 75 males (13 with fragile X syndrome, 18 with mental retardation due to other causes, and 44 with no disability). Latency values were obtained for each ear for the positive deflections of waves I (P1), III (P3), and V (P5). Some individuals with mental retardation required sedation. Contrary to previous report, latencies obtained for individuals with fragile X did not differ from those obtained for persons without mental retardation. Persons receiving sedation, whether or not their retardation was due to fragile X, had longer latencies for wave P5 than persons who did not receive sedation. This effect of sedation may also explain the previously reported increased latencies for persons with fragile X. Am. J. Med. Genet. 74:167–171, 1997.

KEY WORDS: fragile X; brainstem auditory evoked response

INTRODUCTION

Over the last several years, fragile X syndrome has been recognized as the most common hereditary form of mental retardation. Most males with the fragile X syndrome have been reported to be mentally retarded with the degree of retardation ranging from mild to profound [Harvey et al., 1977; Turner et al., 1980; Herbst et al., 1981; Chudley et al., 1983], the largest proportion being within the ranges of moderate to severe [Brown et al., 1987]. Persons with fragile X syndrome also present with behavior disorders, including cases described clinically as autistic disorder [Brown et al., 1982; Hagerman et al., 1986; Cohen et al., 1988; Cohen et al., 1991; Cohen, 1992] and attention deficit disorder [Hagerman and Smith, 1983; Hagerman et al., 1985]. They may also exhibit deviant communication, both verbal [Sudhalter et al., 1990; Sudhalter et al., 1992] and nonverbal [Cohen et al., 1988; Cohen et al., 1991], that appears to be specific to persons with fragile X mental retardation.

While these behavioral and communication disorders may be associated with higher cortical dysfunction, it is important to rule out peripheral and subcortical abnormalities. Frequent ear infections that may result in hearing loss have been reported [Hagerman et al., 1987]. This may explain the presence of impaired hearing, but it is unlikely to account for syndrome-specific behavioral and language abnormalities. If there are abnormalities of language specific to the fragile X syndrome, pathophysiologic correlates, such as atypical subcortical auditory processing, may be present.

Abnormal brainstem auditory evoked responses (BAERs) have been observed in persons with fragile X syndrome [Gillberg et al., 1986; Arinami et al., 1988; Wisniewski et al., 1991]. Arinami et al. [1988] were the only investigators, however, who included a comparison group in their study. They compared the BAERs of 12 males with fragile X syndrome to those of 12 males with no disability. As compared to the nondisabled group, the fragile X group had longer wave V latencies, and prolonged III-V interpeak intervals.

It is important to determine if there are auditory processing deficits specific to fragile X syndrome. Developing effective educational interventions relies on such knowledge. Thus, in the present study we compared the BAER results of males with fragile X syndrome to those of not only persons without any disability, but also to those from individuals with mental retardation due to other causes.

SUBJECTS AND METHOD

Subjects

We studied three groups of males: 13 with fragile X mental retardation (FMR), 18 controls with other mental retardation (OMR) of nongenetic etiology, and 44 nondisabled controls (NDC). Based on clinical and cy-

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togenetic evaluation, each person in the FMR group was positive for fragile X syndrome. Five persons with FMR and 13 in the OMR group received sedation. All other subjects were tested without sedation. Although a one-way ANOVA did not indicate a difference in the mean ages across groups ($F(2,72) = 2.81$, $P > .05$), the FMR group tended to be older than the other two groups. Table I outlines the ages within each group.

The FMR and OMR groups were composed of outpatients of the George Jervis Clinic who had received complete medical and neurological evaluations. All diagnostic data were derived from these clinical evaluations and from reports of psychological evaluations completed not more than three years prior to the current BAER evaluation. Where available, levels of mental retardation, described in Table II, were based on the results of either an IQ test or an adaptive behavior scale. For one case, in the FMR group, level of mental retardation was estimated by using a screening instrument for pediatric cognitive assessment [Shackelford et al., 1980]. Subjects with gross neurological disorders or systemic disease that might affect the BAER were excluded from the study. The nondisabled group were paid volunteers with no history of medical, neurological, or psychiatric problems, recruited from family and friends of the institute staff. The study was limited to persons with BAER thresholds within 11 dB (2 standard deviations) of the laboratory mean to rule out latency differences caused by hearing deficits.

Methods

When required, sedation by orally administered chloral hydrate or intravenous sedation monitored by an anesthesiologist was used. Sedation sufficient to suppress gross movement was accomplished using one or more of the following agents: thiopental, fentanyl citrate (Sublamaze), diazepam (Valium), or droperidol. The duration of sedation was less than one hour. Because of the variability in agent and dosage, individuals were classified simply as sedated or unsedated.

Testing took place in a sound attenuated, temperature and humidity controlled, electrostatically shielded room (2.4 × 2.3 × 2.0 m). Recordings were obtained from Beckman electrodes applied to forehead and left and right mastoids, with a ground applied to the forearm. Electrode resistance was below 5 kohms. Stimuli consisted of 0.1 ms square wave rarefaction clicks, and averages were based on 1,500 responses. Signals were recorded using Grass 511K amplifiers with a gain of 500,000 with frequency band pass of 0.1 kHz-3kHz. Signals were digitized for 12.8 ms at a rate of 10 kHz per channel with a 12 bit resolution, using a PDP11-23 computer. An artifact rejection algorithm was used to eliminate overload conditions. White noise, 30 dB below click intensity, was presented contralaterally as a masking stimulus. Each ear was tested separately.

TABLE I. Subject Ages

Group	Age (yrs) Mean	SD	Range
Nondisabled	12.8	3.0	7–18
Fragile X MR	16.5	8.1	2–28
Other MR	11.5	9.0	1.5–27

TABLE II. Distribution of Subjects with Mental Retardation by Level of Retardation

Level of retardation	Frequency (N) Fragile X MR	Other MR
Profound	0	2
Severe	6	4
Moderate	5	2
Mild	2	10

BAER threshold was defined as the lowest intensity at which wave V was discernible, as determined by presenting a descending series of intensities from 110 dB (peak equivalent SPL) in 20 dB steps followed by an ascending series in 10 dB steps. This procedure has been shown to yield BAER thresholds within 6 dB of behavioral thresholds [Pratt and Sohmer 1978]. Thresholds were obtained using a click rate of 29/s.

After threshold determination, latency values were obtained by testing each ear at an intensity of 50 dB above threshold with a click rate of 10.3/s. Positive deflections of waves I (P1), III (P3), and V (P5) were obtained. In Figure 1, which shows a typical BAER from a male with fragile X syndrome, the three forehead positive potentials studied here are labeled from P1 to P5 and plotted upwards. The click was presented at the earphone at zero time.

RESULTS

Thresholds

Mean BAER thresholds were 50.9, 52.5, and 54.2 dB (peak-equivalent sound pressure level) for the NDC, OMR, and FMR groups, respectively. Thresholds for each ear were analyzed by ANCOVA [Systat, 1991], covarying for age and sedation condition. This analysis revealed no significant differences between groups or between left versus right ear.

Latencies

Analyses of the BAER latencies for waves P1, P3, and P5 were done separately for the data from each ear, each using a 3 (group) × 3 (peak) analysis of variance [Systat, 1991] with covariation for BAER thresh-

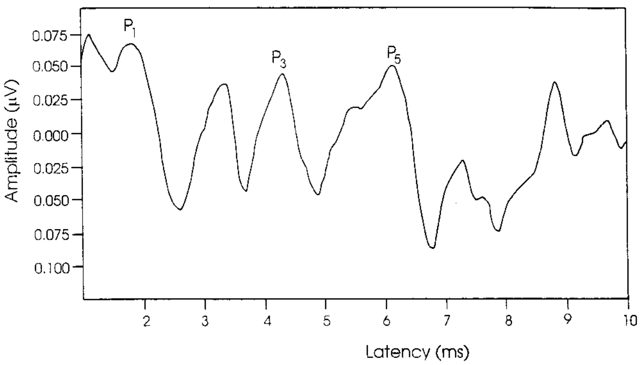

Fig. 1. A typical BAER to right ear stimulation with left ear white noise masking in a 17-year-old male with fragile X syndrome.

old, age, and sedation. Again, groups were FMR versus OMR versus NDC. Neither analysis indicated any significant group effect or interaction. In both of these analyses, sedation accounted for the largest proportion of the total variance contributed by the three covariates. Means and SDs of the latencies observed in the three groups for each ear at each peak are presented in Table III.

Latencies: Sedated Subjects

To examine the effects of sedation, additional analyses compared the FMR and OMR groups, subdivided according to sedation condition. The NDC group, which did not include any persons who were sedated, was excluded from this analysis. Again separately for each ear, the data were analyzed via 2 (group) X 2 (sedation condition) X 3 (peak) analyses of variance [Systat, 1991] with covariation for BAER threshold and age. The analysis of the left ear data indicated no significant effects of group, sedation condition, or any interactions. The analysis of the right ear data indicated a significant sedation condition X peak interaction ($F(2,24) = 5.13, P < .05$). This interaction, confirmed by a significant linear trend across peaks, $F(1,25) = 10.622, P < .005$), indicated that the rate of increase in latency from P3 to P5 with right ear stimulation was greater in the sedated than in the unsedated groups.

Because we were interested in comparing our results to those of Arinami et al. [1988], who compared only latencies averaged across both ears, we performed an analysis to examine interaural latency differences. This was done by using an analysis of covariance in which the effects of covariates may be either fixed or changing, but not both [StatSoft, 1991]. The latency data for both ears were analyzed via a 2 (group) X 2 (sedation condition) X 2 (ear) analysis of covariance with repeated measures and with covariation for BAER thresholds that changed across ears. Only the FMR and OMR groups were compared. Again, since the NDC group did not include any persons who were sedated, it was excluded from this analysis. The analysis was done separately for each peak, using a Bonferroni correction for the number of tests for each peak (.05/3 = .017). A significant effect of sedation condition at P5 ($F = 8.76$, $P = .006$) indicated longer P5 latencies with sedation (mean = 6.03 ms, SD = .163) than without sedation (mean = 5.83 ms, SD = .225). The absence of a sedation condition X ear interaction indicated that the average of the P5 latencies for both ears, the same measure used by Arinami et al. [1988], was longer with sedation. As portrayed in Figure 2, Arinami et al. [1988] observed a difference in latency of the P5 wave between persons with fragile X syndrome (some of whom were sedated) and nondisabled controls (presumably none of whom were sedated). In the same figure, comparison of our results for persons with fragile X syndrome with not only a nondisabled comparison group, but also with a group of persons with mental retardation due to other causes, indicated that the effect may be associated with sedation rather than diagnostic classification. No other effects or interactions were significant.

DISCUSSION

The present results do not support the results of Arinami et al. [1988], who noted longer P5 latencies and longer P3-P5 interpeak latencies in males with fragile X syndrome, without any change in the early components of the BAER (P1 and P3). In the present study, some persons in both our fragile X group and our OMR comparison group required sedation during BAER testing. BAERs of those who required sedation differed from those who did not. Arinami et al. [1988] noted that some of their patients with fragile X syndrome were sedated during BAER testing, whereas their comparison group appeared to include only individuals who had not been sedated. The difference between our sedated and unsedated patients, irrespective of diagnosis, mimics the difference Arinami et al. [1988] reported between their fragile X group, some of whom were sedated, and their comparison group, presumably none of whom were sedated.

Previous studies have demonstrated small, but reliable increases in BAER latencies with sedation. In studies with persons without developmental disabilities, increased BAER latencies have been revealed by within subject comparisons for waves P3 and P5, but not P1, when using either enfluorane, halothane, isoflurane, or pentobarbital for anesthesia [Dubois et al., 1982; Thornton et al., 1984; Manninen et al., 1985; Drummond et al., 1987], and also a smaller increase in the latency of wave P1 when using high doses of sodium thiopental [Drummond et al., 1985]. Sedation was used in the present study to suppress movement artifacts and, as dictated by clinical judgment, consisted of different agents for different patients, thereby complicating comparison of the present results with those of the previous studies. The present study does not resolve whether the longer P5 latencies of persons requiring sedation is related to a characteristic of the individual requiring sedation to reduce movements or due to sedation per se. The relative difference in latencies observed here for those requiring sedation, however, was less than the effect of sedation observed

TABLE III. Latency Means by Group

	Nondisabled				Fragile X MR				Other MR			
	Left ear		Right ear		Left ear		Right ear		Left ear		Right ear	
Peak	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
P1	1.78	.15	1.81	.17	1.79	.21	1.78	.16	1.79	.16	1.79	.18
P3	3.86	.18	3.92	.18	3.96	.21	4.03	.23	3.98	.19	3.98	.23
P5	5.69	.19	5.79	.21	5.98	.16	5.95	.31	5.89	.23	5.97	.23

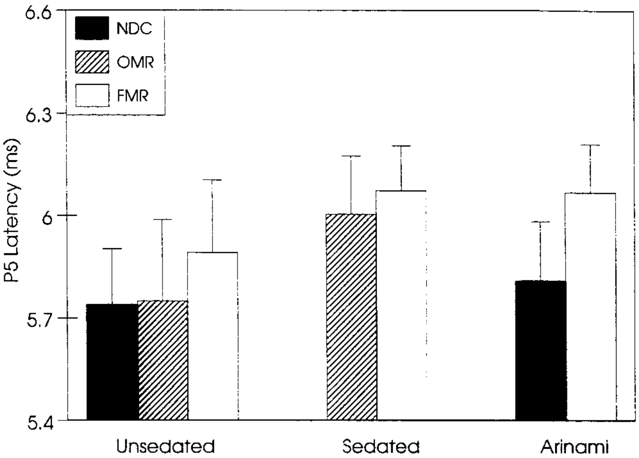

Fig. 2. Mean BAER latency for peak P5, as a function of group and sedation condition, as reported here, and as a function of group as reported by Arinami et al. [1988]. NDC = Nondisabled Comparison; OMR = Other Mental Retardation; FMR = Fragile X Mental Retardation. Vertical bar represents one standard deviation.

within individuals in the previous studies. Since sedation alone does reliably increase BAER latencies, it can be argued that the relatively small difference between the two conditions in the present study was not due to characteristics associated with the need for sedation, but due to sedation per se.

Another limitation of the present study was the presence in the OMR comparison group of more persons with higher cognitive function than in the FMR group. Since the present study was based on a survey of BAER results from a clinic population, it was not possible to match exactly those in the comparison group to those in the FMR group. Further study using groups selected to match their clinical characteristics more precisely and comparing the effects of sedation on a within-subject basis is recommended.

We conclude that the BAER of persons with fragile X syndrome is no different from that observed for persons with mental retardation due to other causes. Of course, there may be exceptions. Persons with fragile X syndrome have longer BAER latencies than individuals with Down syndrome [Miezejeski et al., 1992]. This difference, however, is due primarily to the decreased BAER latencies of persons with Down syndrome, a frequently reported finding [Squires et al., 1980; Squires et al., 1982; Galbraith et al., 1983; Squires et al., 1986; Widen et al., 1987; Miezejeski et al., 1994]. The difference in BAER latencies between persons with Down syndrome and persons with mental retardation due to other causes, including fragile X syndrome, raises a methodological issue that is not restricted to the present context. As previously noted [Miezejeski et al., 1992], when exploring behavioral and pathophysiologic differences across subgroups of mental retardation, choice of comparison group may be an important consideration. Researchers should take into account the presence of specific differences in cerebral function across subgroups of mental retardation. Failure to do so could lead to unwarranted conclusions and misdirection.

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